Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"5792850".PN.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/07 16:38
L2	33	tccr or wsx1 or il27r or (interleukin adj "27" adj receptor) or (t adj cell adj cytokine adj receptor)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/07 16:50
L3	0	class adj I adj cytokinase adj receptor	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/07 16:49
L4	2	"20030008343"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/07 16:49
L5	10	baumgartner-j$.in. and foster-d$.in.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2005/03/07 16:50

***605350** Links

T-CELL CYTOKINE RECEPTOR

Alternative titles; symbols

TCCR
WSX1
INTERLEUKIN 27 RECEPTOR; IL27R

Gene map locus 19p13.11

TEXT

CLONING

Sprecher et al. (1998) searched an EST database for sequences similar to the class I cytokine receptor gp130 (600694). They identified a cDNA encoding a class I cytokine receptor, which they designated WSX1, from an infant brain cDNA library. Using a homology screen, Chen et al. (2000) identified TCCR (T-cell cytokine receptor), a type I cytokine receptor family member identical to WSX1 and most homologous (26% identity; 37% similarity) to IL12RB2 (601642).

By screening a peripheral blood leukocyte (PBL) library, Chen et al. (2000) isolated a full-length cDNA encoding a deduced 636-amino acid TCCR protein. Sequence analysis predicted a single transmembrane domain, a WSX signature motif, and 7 potential N-glycosylation sites in its extracellular domain, and a box1 motif in its intracellular region. Mouse Tccr, isolated from a spleen library, is 62% identical to the human sequence. Northern blot analysis revealed expression of a 3.5-kb transcript in human PBL, thymus, and spleen as well as in adult and fetal lung. Real-time PCR analysis of mouse splenocytes revealed highest expression in CD4 (186940)-positive T cells and in natural killer cells. Among CD4-positive T cells, expression was highest in undifferentiated (Th0) cells, with reduced expression in Th1 and Th2 cells.

GENE FUNCTION

By screening cells expressing members of the IL6 (147620)/IL12 (see IL12B; 161561) family of signaling receptors and coimmunoprecipitation experiments, Pflanz et al. (2002) demonstrated that only WSX1 binds to IL27, a heterodimer consisting of IL30 (608273) and EBI3 (605816).

Takeda et al. (2003) showed that STAT1 (600555) interacted with a conserved cytoplasmic domain tyrosine residue of WSX1 after the residue was phosphorylated. IL27 stimulation induced phosphorylation of STAT1 and expression of TBET (TBX21; 604895) and IL12RB2 in wildtype, but not WSX1-deficient, naive CD4-positive T cells. Together with IL12, IL27 augmented IFNG secretion in wildtype, but not WSX1-deficient, naive CD4-positive T cells. Takeda et al. (2003) concluded that the IL27-WSX1 signaling system acts before the IL12R system in STAT1-mediated TBET induction during the initiation of Th1 differentiation.

Pflanz et al. (2004) found that transfection of WSX1 into a cell line expressing gp130 but only low levels of WSX1 resulted in IL27-dependent phosphorylation of STAT1 and STAT3 (102582). In addition, they showed that anti-gp130 blocked IL27-mediated cellular effects. Quantitative PCR analysis indicated that, in addition to naive CD4-positive T cells, numerous cell types expressed both gp130 and WSX1, including mast cells. IL27 stimulation of mast cells resulted in upregulation of proinflammatory cytokine expression. Pflanz et al. (2004) concluded that IL27 not only contributes to the development of an adaptive immune response through its action on CD4-positive T cells, but also directly acts on cells of the innate immune system.

MAPPING

Sprecher et al. (1998) mapped the WSX1 gene to chromosome 19 by PCR analysis of a somatic cell hybrid panel. They refined the localization to 19p13.11 by linkage analysis using a radiation hybrid panel.

ANIMAL MODEL

CD4-positive helper T cells differentiate into Th1 cells, which are critical for cell-mediated immunity, predominantly under the influence of IL12. IL4 (147780) influences their differentiation into Th2 cells, which are critical for most antibody responses. Mice deficient in these cytokines, their receptors, or associated transcription factors have impaired, but not absent, Th1 or Th2 immune responses. Chen et al. (2000) generated Tccr-deficient mice by gene targeting and showed that these mice have intact or enhanced Th2 phenotypes, as assessed by IL4 production. Tccr-deficient mice are viable, fertile, and display no overt abnormalities. Although intrinsic IFNG (147570) production is normal in response to nonspecific stimulation with lipopolysaccharide, Th1 responses, as measured by IFNG production in response to immunization with keyhole limpet hemocyanin or IFNG-dependent production of IgG2a antibodies in response to ovalbumin, are severely impaired. In addition, infection of control and Tccr-deficient mice with the intracellular pathogen Listeria monocytogenes resulted in bacterial titers that were a million-fold higher in livers of Tccr-deficient mice. The observed Th1 deficiency did not appear to be a result of a defect in the IL12 receptor, as both subunits of the receptor were expressed normally in activated T cells, and the cells proliferated in response to IL12 stimulation. Chen et al. (2000) proposed that TCCR and its potential ligand are candidate targets for intervention in Th1-mediated autoimmune disease and allograft rejection.

Yoshida et al. (2001) generated mice deficient in Wsx1 by homologous recombination. Wsx1-deficient mice were apparently normal and healthy. In vitro immunologic analysis showed that the Wsx1 -/- mice had weak IFNG primary responses but normal secondary responses to mitogen compared with wildtype mice. In response to Leishmania infection, mice lacking Wsx1 were more susceptible than wildtype mice and had weak early IFNG responses. The footpads were enlarged with severe ulceration. The phenotype was not as severe as that of Balb-c mice. RT-PCR analysis indicated that high early IL4 levels were maintained in the knockout mice. Infection with the avirulent Mycobacterium bovis BCG resulted in numerous enlarged and poorly differentiated liver granulomas in Wsx1 -/- mice compared

with wildtype. However, there was no significant difference in bacterial numbers or in liver damage as assessed by transaminase levels. Yoshida et al. (2001) concluded that the impact of lack of Wsx1 early in response to infectious agents is significant, but the impact is mitigated by the presence of other cytokines, such as IFNG and IL12, and their receptors in later phases of the infection.

Villarino et al. (2003) found that Wsx1-deficient mice that were infected with the intracellular parasite Toxoplasma gondii established protective T-cell responses, as measured by inflammatory cytokine production. However, the infected Wsx1-deficient mice were unable to downregulate these responses, which led to a lethal T cell-mediated inflammatory disease. The pathology was characterized by excessive Ifng production, persistence of highly activated T cells, and enhanced in vivo T-cell proliferation. Villarino et al. (2003) concluded that WSX1 is not required for generation of IFNG-mediated immunity to T. gondii, but it antagonizes T cell-mediated immune hyperactivity.

Hamano et al. (2003) reported that Wsx1 -/- mice were unable to control the parasitemia after infection with the intracellular pathogen Trypanosoma cruzi, the causative agent of Chagas disease, or American trypanosomiasis. Wsx1-deficient mice also sustained severe liver injury and increased mortality compared with wildtype mice. The pathology was associated with enhanced levels of Th2 cytokines and the inflammatory cytokines Il6 and Tnfa (191160), as well as overproduction of Ifng, which was responsible for the liver lesions. Hamano et al. (2003) concluded that WSX1 suppresses liver injury by regulating production of proinflammatory cytokines and controls parasitemia by suppressing Th2 responses.

REFERENCES

1. Chen, Q.; Ghilardi, N.; Wang, H.; Baker, T.; Xie, M.-H.; Gurney, A.; Grewal, I. S.; de Sauvage, F. J. :
Development of Th1-type immune responses requires the type 1 cytokine receptor TCCR.
Nature 407: 916-920, 2000.
PubMed ID : 11057672

2. Hamano, S.; Himeno, K.; Miyazaki, Y.; Ishii, K.; Yamanaka, A.; Takeda, A.; Zhang, M.; Hisaeda, H.; Mak, T. W.; Yoshimura, A.; Yoshida, H. :
WSX-1 is required for resistance to Trypanosoma cruzi infection by regulation of proinflammatory cytokine production. *Immunity* 19: 657-667, 2003.
PubMed ID : 14614853

3. Pflanz, S.; Hibbert, L.; Mattson, J.; Rosales, R.; Vaisberg, E.; Bazan, J. F.; Phillips, J. H.; McClanahan, T. K.; de Waal Malefyt, R.; Kastelein, R. A. :
WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J. Immun.* 172: 2225-2231, 2004.
PubMed ID : 14764690

4. Pflanz, S.; Timans, J. C.; Cheung, J.; Rosales, R.; Kanzler, H.; Gilbert, J.; Hibbert, L.; Churakova, T.; Travis, M.; Vaisberg, E.; Blumenschein, W. M.; Mattson, J. D.; and 9 others :
IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4+ T cells. *Immunity* 16: 779-790, 2002.
PubMed ID : 12121660

5. Sprecher, C. A.; Grant, F. J.; Baumgartner, J. W.; Presnell, S. R.; Schrader, S. K.; Yamagiwa, T.; Whitmore, T. E.; O'Hara, P. J.; Foster, D. F. :

Cloning and characterization of a novel class I cytokine receptor. *Biochem. Biophys. Res. Commun.* 246: 82-90, 1998.
PubMed ID : 9600072

6. Takeda, A.; Hamano, S.; Yamanaka, A.; Hanada, T.; Ishibashi, T.; Mak, T. W.; Yoshimura, A.; Yoshida, H. :
Cutting edge: role of IL-27/WSX-1 signaling for induction of T-bet through activation of STAT1 during initial Th1 commitment. *J. Immun.* 170: 4886-4890, 2003.
PubMed ID : 12734330

7. Villarino, A.; Hibbert, L.; Lieberman, L.; Wilson, E.; Mak, T.; Yoshida, H.; Kastelein, R. A.; Saris, C.; Hunter, C. A. :
The IL-27R (WSX-1) is required to suppress T cell hyperactivity during infection. *Immunity* 19: 645-655, 2003.
PubMed ID : 14614852

8. Yoshida, H.; Hamano, S.; Senaldi, G.; Covey, T.; Faggioni, R.; Mu, S.; Xia, M.; Wakeham, A. C.; Nishina, H.; Potter, J.; Saris, C. J. M.; Mak, T. W. :
WSX-1 is required for the initiation of Th1 responses and resistance to L. major infection. *Immunity* 15: 569-578, 2001.
PubMed ID : 11672539

CONTRIBUTORS

Paul J. Converse - updated : 8/11/2004
Paul J. Converse - updated : 11/20/2003
Paul J. Converse - updated : 12/11/2001
Paul J. Converse - updated : 11/3/2000

CREATION DATE

Paul J. Converse : 10/18/2000

EDIT HISTORY

terry : 2/2/2005
mgross : 8/11/2004
mgross : 11/20/2003
mgross : 11/20/2003
mgross : 1/8/2002
terry : 12/11/2001
mgross : 11/3/2000
alopez : 10/18/2000